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Breast Cancer Risk in Families with Cleft Lip and Palate

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Abstract

PURPOSE—To test whether females in families with cleft lip and/or palate (CL/P) have increased breast cancer risk

METHODS—Using the Danish Facial Cleft Registry, females with CL/P, mothers of children with CL/P, and sisters to CL/P cases were identified for the Danish birth cohorts 1911 to 1975. These females were compared to a 5% random sample of these cohorts regarding the incidence and age of onset for breast cancer registered in the Danish Hospital Discharge Register 1977–2005.

RESULTS—Examining 48,404 person-years for 1,809 female CL/P cases (49 breast cancer cases) and 212,795 person-years for 7935 female relatives (188 breast cancer cases) we found no increased breast cancer risk for either CL/P cases (hazard ratio (HR) = 1.23, 95% confidence interval (CI): 0.92–1.63), mothers of children with CL/P (HR = 0.93, 95%, CI: 0.80–1.08), or sisters of CL/P cases (HR = 0.94, 95% CI: 0.55–1.60). Neither were there any significant differences in age of onset.

CONCLUSION—Both epidemiological and genetic studies have suggested common etiological factors for breast cancer and cleft lip and/or palate (CL/P). However, this population-based study was not able to confirm a general increase in breast cancer risk among females in families with CL/P.

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Keywords

Cleft lip; cleft palate; breast cancer; recurrence; family study

INTRODUCTION

Congenital malformations and cancer may share common etiological factors (1–3). Co-occurrences of malformations and cancers have been seen in children due to both genetic and environmental causes. Genetic links between malformations and cancer include mutations in the Patched Homolog 1 (*PTCH*) gene which produce physical anomalies such as rib and craniofacial abnormalities, and basal cell carcinoma or medulloblastoma (4–6). Mutations in the Wilms Tumor 1 (*WT1*) gene or Paired Box 6 (*PAX6*) gene can lead to WAGR syndrome, which is characterized by Wilm's tumor associated with genitourinary, diaphragmatic, and ocular physical abnormalities (7). Another well studied example is between Down syndrome and leukemia (8, 9).

Cleft lip and/or palate (CL/P) is a common congenital malformation, with a frequency of approximately one per 700 births, but varying widely by race (2, 10). CL/P can be divided into subphenotypes based on their anatomical location with common subdivisions including cleft lip only (CL), cleft lip with cleft palate (CLP) and cleft palate only (CP) (11, 12). While CL and CLP have been commonly lumped into cleft lip with or without cleft palate, evolving evidence suggests they can have distinct and independent risks (13–15). Danish twin studies have found a monozygotic twin concordance rate between 40–60% for CL/P while dizygotic twins have a concordance rate of approximately 5–10% with heritability estimates of 70–90% (16–19), suggesting that genetic factors play a major role in the susceptibility to CL/P.

Several studies have found associations between CL/P and various cancers for affected individuals (20–23) and in their families (24, 25). Other studies have failed to find an association between CL/P and cancer (26). A general problem for many previous studies is small sample sizes of both cancer and CL/P cases. A previous study in Denmark that examined the co incidence of CL/P with all types of cancers reported an increased breast cancer occurrence in female CL/P cases (20). This observation is particularly interesting because recent findings suggest common underlying genes for craniofacial development and breast cancer risk: Breast cancers have been found to express high levels of Fibroblast Growth Factor 2 (*FGFR2*), and certain genetic variants of *FGFR2* predispose an individual to cancer (27–32). *FGFR2* is also important in craniofacial development and has been implicated in the development of CL/P (33–35). Furthermore, some *FGFR2* mutations have been associated with CP in individuals with Apert syndrome (36). A recent genome wide association study of CL/P also identified the *MAFB* gene as having alleles contributing to CL/P (37) and *MAFB* has also been associated with certain hematologic malignancies (38). This study examines the association between CL/P and breast cancer in more than 1,800 female CL/P cases and nearly 8,000 first degree female relatives to CL/P cases, accounting for over 250,000 follow-up years.

METHODS

Study design

The risk of cancer in families with CL/P was examined using data from Danish Facial Cleft Registry (39), the Central Population Register (39, 40), and the Danish Hospital Discharge Register (41).

The Central Population Register—This register was established in 1968. It includes all persons who have had a permanent residence in Denmark since April 2, 1968. Each person registered receives a unique identification number which enables accurate linkage between that individual and all other national registers. Information contained in this registry includes name, sex, date of birth, and vital status (alive, dead, or emigrated). Link between parents and offspring is available for nearly all persons born 1960 or later and to some degree for individuals born 1953–59. This link enables the identification of first degree relatives to the cleft cases (39).

The Danish Hospital Discharge Register—This register contains data on all somatic hospital admissions since 1977, and on all outpatients and emergency patients since 1995. Diagnostic information is classified by the Danish version of the International Classification of Disease versions 8 and 10. Cancer occurrence was identified from the register. Males were excluded due to the low incidence of breast cancer among men (20).

The Danish Facial Cleft Register—This register includes children with facial clefts born in Denmark from 1936 to 2006. Nearly all (99%) of live-born cleft cases without associated malformations have been ascertained, except for submucous cleft palate defects, which often remain asymptomatic (40, 42, 43). Only non-syndromic clefts are considered in this study, as syndromic clefts often have different genetic etiologies. In the Danish Facial Cleft Database 876 (9.6%) of the individuals born with a CL/P are registered as also having at least one non-cleft major anomaly or a recognized syndrome. For the earlier birth cohorts from 1936 to 1987 the number of individuals born with either an associated major anomaly or a syndrome was likely underestimated (40) but for the later birth cohorts medical records were reviewed by Bille et al. in 2005 to obtain more complete information about associated anomalies/syndromes (20, 44). The recorded number of associated anomalies/syndromes are slightly lower in the Danish population compared to other populations (45, 46), but the pattern with more anomalies/syndromes associated with CP compared to CL/P is the same.

Study Population—The CL/P cases born in Denmark 1936 to 2006 were used to identify mothers and sisters to CL/P cases, but only those CL/P cases born 1936 to 1975 were included in the breast cancer occurrence analyses since breast cancer before age 30 is extremely rare. The study population for breast cancer occurrence comprised 1,809 cleft cases, 5,592 mothers of children with clefts, and 2,343 sisters who had a sibling with a cleft. These subjects were born in Denmark between 1911 and 1975, and were alive in Denmark on January 1st 1977. Similar inclusion criteria applied to the 5% random sample and their first degree relatives. 1911 was chosen as the birth year entry date, as there were few informative subjects born earlier. The follow-up period was from January 1, 1977, corresponding to the beginning of the Danish Hospital Discharge Register, until December 31, 2005. The personal identification number was used to make a linkage between the Hospital Discharge Register and the Cleft Register.

Statistical Analysis

Data were grouped by five calendar-year birth cohorts and cleft type. Cox proportional hazards regression models with the first breast cancer diagnosis as the event of interest and the observation time from 1977 until breast cancer diagnosis, death, emigration out of Denmark, or the end of the study (December 31, 2005) were used to compare the cleft population with the reference population. The Cox models were built using age as the time scale (47). We first compared aggregate CL/P status to the reference sample and then compared different cleft types (CL, CLP, and CP) with reference samples for the three subgroups (cleft cases, mothers, and sisters), e.g. the mothers of CL/P cases born 1936–2006 were compared to the mothers of the individuals in the 5% random sample who were born

1936–2006. Another model combined CL with CLP, as they can have a similar genetic origin (48). Mothers and sisters who had multiple cleft type children/siblings were excluded (N=12), except in the combination CL and CLP, where mothers and sisters with children/siblings of both those two types were included. The final model for all tests used age as the time scale with the cleft status and calendar year birth cohort as variables. Interactions and proportional hazards fitting were tested in all models.

To control for possible errors in data entry of breast cancer diagnoses into the Danish Hospital Discharge Register, surgical procedural codes for breast cancer were used as verification of the diagnosis. In other words, in a subanalysis only women who received both a discharge diagnosis of breast cancer and had a surgical code that related to the removal of a breast cancer were included.

To assess the effect of a cleft history on an individual's time to develop breast cancer, the mean age of individuals who developed breast cancer was compared using the Wilcoxon rank-sum test, as the data were not normally distributed. This test was performed on CL/P overall as well as the cleft subtypes.

RESULTS

Women born with an CL/P accounted for 48,404 person years of follow-up, mothers of children born with clefts accounted for 150,305 person years of follow-up, and sisters whose siblings were born with clefts accounted for 62,490 person years of follow-up (Table 1). The distribution of cleft types differs between the cases (all female cases and therefore a large proportion of CP, which is more common in females (20)), and mothers/sisters to cleft cases (both male and female cases and hence fewer CP). The mean age for the cleft group was 46 years, 1.5 years younger than the mean for the reference sample group which was a significant difference ($p<0.001$). The mean age for the mothers of clefts group was 37.6 years old, 0.2 years younger than the reference population group, which was not statistically significant ($p=0.32$). The age range 0–49 accounted for 49% of the cancer follow-up time for clefts, 28% for mothers, and 93% for sisters (Table 2).

The sex distribution for each cleft subtype is in accordance with known distributions (20). Mothers to male children with clefts are overrepresented in the CL and CLP groups, while mothers to female children with clefts are overrepresented in the CP group. When adjusting for birth cohort and age in Cox proportional hazards regression models, CL/P was not significantly associated with breast cancer for any of the three subject groups (Table 3). Women born with clefts showed a trend toward increased risk while mothers and sisters had a trend toward lower risk for breast cancer. No interactions between birth cohort and cleft status were significant. All models fit the proportional hazards assumption. Stratifying the analyses for cleft sub-types did not reveal any consistent pattern (Table 3): In affected cases, CLP was associated with increased risk for breast cancer, while for mothers CLP was significantly associated with decreased risk and CP was associated with increased risk. No cleft types were significantly associated with breast cancer occurrence in the sister group.

Surgery codes were used to verify the validity of the discharge diagnoses of breast cancer. There were 785 (10.7%) women total from the three groups, both reference population and cleft case population (Clefts: Reference = 182 (10.5%), Case = 5 (10.2%); Mothers: Reference = 529 (10.8%), Case = 27 (15.5%); Sisters: Reference = 40 (8.7%), Case = 2 (14.3%)), who appeared in the Hospital Discharge Registry but who did not have a surgical code for breast cancer. The removal of these women made the mother group cleft palate result non-significant (Table 4). No other results were appreciably affected. Also, removal of 250 mothers who had CL/P from the mother group did not affect the model results.

No significant differences in age at breast cancer diagnosis between CL/P family individuals and reference population individuals were found overall or for any of the three groups (Clefts p=0.34; mothers p=0.14; sisters p=0.10). In the mother group, CP was borderline associated with a younger age of onset in the mothers of cleft cases (p=0.07). In the sister group, the combination of CL with CLP was borderline associated with an older age of onset for sisters of cleft cases (p=0.06).

DISCUSSION

Analyses of the occurrence of breast cancer in more than 1,800 CL/P cases and almost 8,000 first degree relatives showed no association between breast cancer risk when all nonsyndromic CL/P types were analyzed together. Cleft subtype analysis revealed some associations, but none were consistent across all groups. For individuals with CLP an increased risk of breast cancer was found, which is in agreement with the trend found by Bille et al, 2005, that is based on a fraction of the present CL/P study population (20). Having a child with isolated CP was associated with an increased risk of breast cancer for the mother, while having a child with CLP was associated with lower risk. The different (and apparently counterintuitive) effects of these cleft types may be biologically plausible, since there is evidence that the different cleft types have different genetic origins (13, 15), but they may also reflect random findings in multiple testing or differences in parent of origin effects on different cleft types. We were unable to assess parent of origin contributions in this study.

The association between CL/P and breast cancer was also examined by comparing the times of onset for breast cancer for CL/P cases and the reference population. This showed no significant differences in the onset times between women with and without these family histories. The mean age among CL/P cases was expected to be slightly lower than among the reference population due to higher mortality among CL/P cases (49).

A limitation in the study is the left and right truncation. Cancer death and cancer treatment completed before 1977 are not included, but this apply both to the CL/P groups and the reference groups, and our analyses do not indicate that the CL/P groups have earlier onset. The right truncation is most pronounced for the sisters for whom most of the risk time is before age 50 and therefore with limited power.

Previous studies

Several studies of CL/P and cancer focus on the risk of childhood cancer, where associations have been found (21,23). However, there are relatively few studies that examine the effects of CL/P later on in life when breast cancer occurs. The present study is an extension of the study by Bille et al, 2005 (20).This study was on CL/P cases only and, based on linkage to the Danish Cancer Registry (50), it found that CL/P was associated with an increased breast cancer risk and each subtype was non-significantly trending toward increasing risk. However, the present extended and more powerful study could not confirm this.

Zhu et al, 2002 (24) found in a Danish study that a family history of CL/P was associated with an increased risk of cancer, but was based on only 6 cases of cancer in mothers of children with clefts. Menezes et al, 2009 (25) also found that a family history of CL/CLP was associated with an increased risk for breast (as well as some other) cancers, while our study found that CL/CLP was associated with a decreased risk in mothers. The study by Menezes et al. was performed in the United States and had a smaller sample size (70 families with cases of cancer in the family). Steinwachs et al, 2000 (26) examined CL/CLP and found no association between clefting and familial cancer risk.

The hypothesized association between breast cancer and CL/P could be due both to genetic factors and/or familial environmental factors that are both teratogenic and carcinogenic. Another possibility could be that having a cleft leads to social marginalization and changes in lifestyle that predisposes an individual and their family to cancer (i.e. smoking, high alcohol use, etc) (20, 51, 52).

Breast cancer is associated with environmental risk factors such as nulliparity and late age at first delivery (53). These factors have been hypothesized as at least a partial explanation for associations between breast cancer and CL/P (20). Individuals who have CL/P are less likely to have children and when they do have children they have them later in life (54, 55). This is a possible explanation, but only for individuals with clefts, and despite this bias towards higher cancer occurrence in CL/P cases, we did not find general evidence for an association.

Abbreviations

CL/P	cleft lip and/or palate
CL	cleft lip
CLP	cleft lip and palate
CP	cleft palate

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Table 1

Danish Female Cleft Cases, Mothers and Sisters of Cleft Cases and Reference Population Born 1911 Through1975 and Followed in the Hospital Discharge Register From 1977 Through 2005

	Cleft Cases	Reference	Mothers of Cleft Cases	Reference	Sisters of Cleft Cases	Reference
Total	1,809	69,334	5,592	143,559	2,343	60,791
Breast Cancer Cases	49	1740	174	4890	14	460
Cleft Type						
Cleft lip	513		1,726		733	
Cleft lip + palate	536		2,114		893	
Cleft palate	760		1,715		706	

Table 2

Sample Size, Breast Cancer Cases, and Person-years of Follow-up by Birth Cohort for Female Cleft Cases, Mothers and Sisters of Cleft Cases and Background Population

	Birth Cohorts								
	1911–1936	**1935–1940**	**1941–1945**	**1946–1950**	**1951–1955**	**1956–1960**	**1961–1965**	**1966–1970**	**1971–1975**
Cleft Cases	0	143(11)*	198(9)	210(11)	225(11)	241(3)	256(1)	268(1)	268(2)
		9185	11991	11742	11314	10709	10303	9528	8123
Reference	0	6981(407)	8858(482)	9485(392)	8600(219)	8429(127)	9293(76)	8977(30)	8711(7)
		454627	535171	530003	436100	380051	371055	314952	262326
Mothers of Cleft Cases	1023(59)	577(39)	675(27)	682(26)	631(13)	623(6)	624(3)	476(1)	281(0)
	74688	37395	40872	38419	32454	28642	25446	17285	8947
Reference	27073(1765)	14589(880)	17619(883)	17739(689)	15117(349)	14790(199)	15991(81)	12862(42)	6879(2)
	2044829	951551	1068989	995981	772550	675300	647900	463353	215788
Sisters of Cleft Cases	0	0	4(0)	11(0)	113(6)	382(4)	612(4)	628(0)	593(0)
			246	624	5540	17046	24250	22354	18093
Reference	0	0	110(4)	315(9)	3087(82)	10790(153)	16364(96)	15492(48)	14633(14)
			6692	17612	151707	480697	652221	545239	443225

*Number of subjects (# of cancers) – person years of follow-up

Table 3

Risk of Breast Cancer (Hazard Rate) adjusted for Birth Cohort

Cleft Type	Cleft Cases	Mothers	Sisters
Aggregate (all Cleft Cases)	1.23 (0.92–1.63)	0.93 (0.80–1.08)	0.94 (0.55–1.60)
CL	0.72 (0.36–1.44)	0.84 (0.63–1.11)	0.62 (0.20–1.92)
CLP	**1.84 (1.21–2.79)**	**0.74 (0.56–0.97)**	0.87 (0.36–2.10)
CP	1.13 (0.72–1.78)	**1.29 (1.03–1.63)**	1.41 (0.63–3.15)

Results in bold are significant ($P < 0.05$)

Table 4

Risk of Breast Cancer (Hazard Rate) adjusted for Birth Cohort – Only Subjects With Both Discharge Diagnosis and Surgical Code for Breast Cancer

Cleft Type	Cleft Cases	Mothers	Sisters
Aggregate	1.23 (0.91–1.66)	0.88 (0.75–1.04)	0.89 (0.50–1.58)
CL	0.70 (0.33–1.47)	0.84 (0.62–1.13)	0.46 (0.11–1.83)
CLP	**1.77 (1.12–2.78)**	**0.66 (0.48–0.89)**	0.77 (0.29–2.07)
CP	1.20 (0.75–1.90)	1.23 (0.96–1.58)	1.56 (0.70–3.50)